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EXAMINER

SHIBUYA, MARK LANCE

ART UNIT PAPER NUMBER

1639

DATE MAILED: 02/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

09/601,644

Applicant(s)

GARIEPY ET AL.

Examiner

Mark L. Shibuya

Art Unit

1639

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 21 November 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-7, 9-18, 20, 24, 25 and 27-43 is/are pending in the application.
- 4a) Of the above claim(s) 17, 18, 20, 24, 25 and 27-41 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-7, 9-16, 42 and 43 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)             | 4) <input type="checkbox"/> Interview Summary (PTO-413)                     |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)    | Paper No(s)/Mail Date. _____  |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____   | 6) <input type="checkbox"/> Other: _____                                    |

### **DETAILED ACTION**

1. Claims 1-7, 9-18, 20, 24, 25, 27-43 are pending. Claims 17, 18, 20, 24, 25, 27-41 are withdrawn from consideration. Claims 1-7, 9-16, 42 and 43 are examined.

#### ***Interview***

2. The applicant's summary of the interview held 10/18/2005, in the Reply entered 11/21/2005, is acknowledged.

#### ***Election/Restrictions***

3. This application contains claims 17, 18, 20, 24, 25, 27-41, drawn to inventions nonelected with traverse in the Paper entered 10/11/2004. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

#### ***Priority***

4. This application is the national stage under 35 U.S.C. 371, of PCT/CA98/01137, filed 12/08/1998. Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). The certified copy of Canadian priority document 2,222,993, filed on Feb. 4, 1998, appears in the instant application papers, and in PCT/CA98/01137, filed 12/08/1998.

***Withdrawn Objections and Rejections***

5. The objection to the Drawings is withdrawn in view of applicant's explanation that Figure 1 is mistakenly grouped with the originally filed claims.

6. The rejection of Claims 1-16 and 42 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, is withdrawn upon further consideration by the examiner.

7. The rejection of claims 1-16 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is withdrawn, in part, in view of applicant's amendments to the claims, entered 3/3/2005.

8. The rejection of Claims 1-3, 5, 8-13, and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Jackson et al., J. of Bacteriology, Feb. 1990, Vol. 172, No. 2, pp. 653-658, (previously cited), is withdrawn in view of applicant's arguments and amendments to the claims, entered 3/3/2005.

9. The rejection of Claims 1-3, 5, 8-13, and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Tyrrell et al., Proc. Natl. Acad. Sci. USA, vol. 89, pp. 524-528, Jan 1992 (IDS filed 11/20/2000), is withdrawn in view of applicant's arguments and

amendments to the claims, entered 3/3/2005. But see below rejections under 35 USC 103(a).

10. The rejection of Claims 1 and 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over either of Jackson et al., J. of Bacteriology, Feb. 1990, Vol. 172, No. 2, pp. 653-658, (previously cited with the Requirement for Restriction/Election, mailed 8/10/04) or Tyrrell et al., Proc. Natl. Acad. Sci. USA, vol. 89, pp. 524-528, Jan 1992 (IDS filed 11/20/2000), each taken separately, and Cheng et al., (US 5,869,250), is withdrawn in view of applicant's arguments and amendments to the claims, entered 3/3/2005. But see below rejections under 35 USC 103(a).

11. The rejection of Claims 1 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over either of Jackson et al., J. of Bacteriology, Feb. 1990, Vol. 172, No. 2, pp. 653-658, (previously cited with the Requirement for Restriction/Election, mailed 8/10/04) or Tyrrell et al., Proc. Natl. Acad. Sci. USA, vol. 89, pp. 524-528, Jan 1992 (IDS filed 11/20/2000), each taken separately, and Reidhaar-Olson et al., Meth Enzymol (1991), vol. 208: 564-586, is withdrawn in view of applicant's arguments and amendments to the claims, entered 3/3/2005. But see below rejections under 35 USC 103(a).

12. The rejection of Claims 1 and 7 rejected under 35 U.S.C. 103(a) as being unpatentable over either of Jackson et al., J. of Bacteriology, Feb. 1990, Vol. 172, No.

Art Unit: 1639

2, pp. 653-658, (previously cited with the Requirement for Restriction/Election, mailed 8/10/04) or Tyrrell et al., Proc. Natl. Acad. Sci. USA, vol. 89, pp. 524-528, Jan 1992 (IDS filed 11/20/2000), each taken separately, and Nickoloff et al., (US 5,354,670), is withdrawn in view of applicant's arguments and amendments to the claims, entered 3/3/2005. But see below rejections under 35 USC 103(a).

13. The rejection of Claims 1, 2, and 13-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over either of **Jackson et al.**, J. of Bacteriology, Feb. 1990, Vol. 172, No. 2, pp. 653-658, (previously cited with the Requirement for Restriction/Election, mailed 8/10/04) or **Tyrrell et al.**, Proc. Natl. Acad. Sci. USA, vol. 89, pp. 524-528, Jan 1992 (IDS filed 11/20/2000), each taken separately, and **Frankel et al.**, (US 4,753,894), is withdrawn in view of applicant's arguments and amendments to the claims, entered 3/3/2005. But see below rejections under 35 USC 103(a).

***Claim Rejections - 35 USC § 112, First Paragraph***

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

14. Claims 1-16, 42 and 43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application

Art Unit: 1639

was filed, had possession of the claimed invention. This rejection is for lack of written description.

This rejection is necessitated by applicant's amendments to the claims. This rejection is maintained for the reasons of record as set forth in the previous Office action. That rejection is copied below for the convenience of the reader.

The claims are drawn to a method for making a cytotoxic mutant protein having a different receptor-binding specificity than the wild type protein, comprising incorporating mutations into DNA encoding the binding domain of a heteromeric protein toxin to produce variant forms of the heteromeric protein toxin, generating a library of clones to produce variant forms of the heteromeric protein toxin, screening against a population of screening cells and selecting a cytotoxic mutant protein that inhibits or kills said population of screening cells to a greater extent than wild-type cytotoxic mutant protein.

Vas-Cath Inc. v. Mahurkar, 19 USPQ 2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See Vas-Cath at page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 116). The claimed genus of cytotoxic proteins is broad and includes species named in the specification and claimed, such as Shiga toxin, Shiga-like toxins, ricin, abrin, gelonin, croton, pokeweed antiviral protein, saporin, momordin, modeccin, sarcin, diphtheria toxin and *Pseudomonas aeruginosa* exotoxin A, as well as other species not described, such as snake, lizard, spider and insect venoms (see, e.g., US Patent No. 6,833,131 at col. 1, lines 10-35; US Publication No. 2002/0161203 A1 at para [0005], [0190]). The specification provides specific embodiments, working or otherwise, only for Shiga-toxin and Shiga-like toxins. In the Specification, at Example 4, pp. 22-23, the method used for producing a cytotoxic mutant protein having a different receptor-binding specificity than the wild type protein appears to rely on using the CAMA-I cell line, because it lacks the CD77 marker that is the receptor for Shiga toxin and Shiga-like toxin (p. 12, lines 16-19). The specification does not disclose cell lines that similarly lack the receptors for the other heteromeric protein toxins that constitute the genus. The examiner respectfully submits that the specification does not provide a representative number of species to show possession over the entire genus claimed. It is noted that the examined claims do not require that the screening cell line lack the receptor recognized by the wild-type toxin.

The specification at p. 25, lines 25-29, states that the "B subunit variants may thus bind to a spectrum of molecular entities such as proteins, peptides, nucleic acids or even organic moieties rather than to sugars or glycolipids (such as CD77)." However, in regard to the embodied species of Shiga-toxin, the specification does not describe what different receptor the mutated B subunit now has specificity for and describes no assays, actual or prophetic, to demonstrate positively that the mutated toxins now have specificity for a different receptor, as claimed. Also, the specification does not disclose that the mutated B subunits do not bind to the CD77; rather that the mutated toxin kills CAMA-1 cells, which the specification teaches lacks CD77, and SKBR-3 cells, which the specification teaches expresses CD77 (Specification at p. 22, lines 4-14). Given the unpredictability of the arts of biology and of mutation, particularly in changing the target of a protein ligand, extrapolation from cytotoxicity data (see Specification at Example 4, pp. 22-23) that the mutated Shiga toxin B subunit has a different receptor-binding specificity is uncertain. The Office does not have the facilities and resources to provide the factual evidence needed in order to determine that the cytotoxic mutant protein has a different receptor-binding specificity than the wild type protein. It is respectfully submitted that the practitioner would not be reasonably apprised that the applicant was in possession of the claimed invention, in regard to the particular species of Shiga toxin or Shiga-like toxin.

Art Unit: 1639

Vas-Cath Inc. v. Mahurkar, 19 USPQ 2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See Vas-Cath at page 1117). See, also, Fiers v. Revel, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481 at 1483. In Fiddes, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 § 112 is severable from its enablement provision.

The applicant argues that amending the claims to recite that the heteromeric protein toxins are ribosome-inactivating protein (RIP) overcomes the instant written description because RIPs are described in the specification and include the Shiga and Shiga-like toxins. The applicant argues that the two breast cancer cell lines described in the specification is representative of the genus of screening cells because the particular cell type used in the claimed method is not critical, provided the combination of toxin and cell type are such that a selection can be made based on an observed increase in toxicity. Applicant argues that an important benefit of the present invention is that it does not require any prior or subsequent knowledge of the specific nature of the receptor. Applicant states:

The screening techniques identifies, via observed toxicity, the mutation that works in combination with some receptor on the screening cells, and neither the nature of the receptor nor the nature of the mutation needs to be known. While it may be interesting to know the type of receptor a new toxin binds to, this is not a reason to say that there is no written description of the invention as claimed.

Reply at p. 11, para 2.

#### Response to Arguments

Applicant's arguments entered, 11/21/2005, have been fully considered but they are not persuasive.

The specification does not provide a representative number of species to show possession over the entire genus of RIP claimed. Heteromeric RIP, as claimed, appear to represent type 2 RIP. The genus of type 2 RIPs include certain plant toxins, such as the lectin ricin, and bacterial toxins, including Shiga toxin and Shiga-like toxin, produced by enterohemorrhagic strains of *Escherichia coli*, as well as other toxins (see Hartley et al., *Biochimica et Biophysica Acta* (2004), 1701, pp. 1-14, and especially p. 2, para 3 and Table 1). The specification as filed includes some of these type 2 RIPs, such as ricin, abrin, momordin, shiga toxin and shiga-like toxin, but does not disclose others, such as volkensin, viscumin, ebulin b, SNAI, SNAV, or SNAIf.

The claims are drawn to selecting mutant proteins with a different binding specificity than the wild type binding protein. Applicant bases this element on the use of the CAMA-1 cell line, which appears to lack the CD77 glycolipid, to which the Shiga toxin and Shiga-like toxin bind, (as taught by the instant specification). It appears that applicant reasons that because the CAMA-1 cell line lacks the CD77 receptor, the mutated toxins must act by having a different receptor binding specificity, i.e., binding to a different receptor. However, the specification does not describe species of cell lines that lack the receptors for different species of the genus of RIPs, other than the CAMA-1 cell line, which is specific for Shiga toxin or Shiga like toxin. For example, there are no described cell lines that are resistant to volkensin, viscumin, ebulin b, SNAI, SNAV, or SNAIf.

The practitioner would not envision that the applicant had process of mutant proteins that have different receptor specificity. Applicant has not identified what

Art Unit: 1639

receptor the mutated Shiga toxin or Shiga-like toxin binds to and therefore, the specification cannot describe it. Roberts et al., Mini Reviews in Medicinal Chemistry (2004) Vol. 4, pp. 505-512, throughout the publication, and e.g., at p. 507, para 2, teach that the RIP ricin, is taken into the cell by endocytosis after binding galactosides on the mammalian cell surface. Roberts et al. states "[t]he precise endocytic route may be influenced by the nature of the surface molecule to which the toxin has bound, and since ricin promiscuously binds to many different surface glycoproteins, it isn't perhaps surprising to find that it can enter by both clathrin-dependent and clathrin-independent endocytosis." Thus the RIP and its mutant protein may have common specificity to one or more of several different receptors. Perhaps a mutant RIP continues to have the same receptor binding specificity, but other pathways are affected or different.

The publication of Battelli, Mini Reviews in Medicinal Chemistry (2004) Vol. 4, pp. 513-521, throughout the publication, and e.g., at p. 513, bridging paragraph and p. 513, para 2, teaches that "[c]omparing the cytotoxicity of various type 2 RIP for a cell line and, conversely, the different sensitivity of various cell lines to the same toxin, it appeared clear that the interaction between cells and RIP was more complicated than it was predictable on the basis of the molecular structure." Battelli states that "[t]he correlation between RIP structure and cytotoxicity had become even less linear when a new category of type 2 RIP emerged, which, in spite of the presence of the lectinic chain, have a low toxicity, similar to that of type 1 RIP (Table 1). . . . For instance, the lower cytotoxicity of nigrin b compared with ricin has been at least in part explained by a higher degradation of nigrin b by cells, with a resulting lower concentration remaining

Art Unit: 1639

inside the cells, and by the different intracellular pathways followed by the two lectins”.

Thus it is clear that the genus of RIPs is heterogeneous, unpredictable, and complicated in the mechanism of action. Therefore, one of skill in the art would not envision that the applicant had possession of the invention as now claimed.

15. Claims 1-7, 9-16, 42 and 43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of for making a cytotoxic mutant protein or pool of Shiga toxin or Shiga-like toxin proteins, does not reasonably provide enablement for making mutants for any heteromeric ribosome inactivating protein with a different receptor binding specificity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. This rejection is necessitated by applicant's amendments to the claims.

There are many factors be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether undue experiment is necessitated. These factors can include, but are not limited to:

- (1) the breadth of the claims;
- (2) the nature of the invention;
- (3) the state of the prior art;
- (4) the relative skill of those in the art;
- (5) the level of predictability in the art;
- (6) the amount of direction provided by the inventor;
- (7) the existence of working examples; and
- (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(1 and 2) The breadth of the claims and the nature of the invention: The claims are drawn to a method for making a cytotoxic mutant protein that is a ribosome inactivating protein,(RIP), having a receptor-binding specificity that is different from the specificity of the wild type RIP, comprising incorporating mutations into DNA encoding the binding domain of a heteromeric RIP toxin to produce variant forms of the heteromeric RIP toxin, generating a library of clones to produce variant forms of the heteromeric RIP toxin, screening against a population of screening cells and selecting a cytotoxic mutant protein that inhibits or kills said population of screening cells to a greater extent than wild-type cytotoxic mutant protein. Thus the claim is broadly drawn to making mutants of any heteromeric RIP toxin. The specification at p. 25, , lines 25-29, states that the "B subunit variants may thus bind to a spectrum of molecular entities such as proteins, peptides, nucleic acids or even organic moieties rather than to sugars or glycolipids (such as CD77)." Therefore, the different receptor to which the variant forms of the mutated cytotoxic protein can bind, is contemplated by the specification to encompass virtually any biological molecule.

(3 and 5) The amount of direction provided by the inventor and the existence of working examples: Applicants have only exemplified the preparation of mutant Shiga toxin, although the example probably is applicable to Shiga-like Toxin-1, as the specification at p. 12, lines 16-19 teaches that both toxins recognize the glycolipid CD77 (also known as Gb<sub>3</sub>). In Example 4, pp. 22-23, the specification provides specific embodiments, working or otherwise, only for method used for producing a cytotoxic

Art Unit: 1639

mutant protein of Shiga-toxin. However, in regard to the embodied species of Shiga-toxin, the specification does not describe what different receptor the mutated B subunit now has specificity for and describes no assays, actual or prophetic, to demonstrate positively that the mutated toxins now have specificity for a different receptor, as claimed. The specification does not disclose the molecule, if any, to which the mutated B subunit of the variant Shiga toxin protein now binds. Also, the specification does not disclose that the mutated B subunits do not bind to the CD77; rather that the mutated toxin kills CAMA-1 cells, which the specification teaches lacks CD77, and SKBR-3 cells, which the specification teaches expresses CD77 (Specification at p. 22, lines 4-14). The specification does not provide guidance or direction for cell lines resistant to RIP other than Shiga toxin or Shiga-like toxin.

(4) The state of the prior art and the level of predictability in the art Methods for making for making mutant Shiga toxin and mutant Shiga-like toxin was known in the art at the time of filing, however, the correlation of RIP receptor specificity to RIP-induced cytotoxicity is unpredictable. The publication of Battelli, Mini Reviews in Medicinal Chemistry (2004) Vol. 4, pp. 513-521, throughout the publication, and e.g., at p. 513, bridging paragraph and p. 513, para 2, teaches that “[c]omparing the cytotoxicity of various type 2 RIP for a cell line and, conversely, the different sensitivity of various cell lines to the same toxin, it appeared clear that the interaction between cells and RIP was more complicated than it was predictable on the basis of the molecular structure.” Battelli states that “[t]he correlation between RIP structure and cytotoxicity had become even less linear when a new category of type 2 RIP emerged, which, in spite of the

Art Unit: 1639

presence of the lectinic chain, have a low toxicity, similar to that of type 1 RIP (Table 1).

... For instance, the lower cytotoxicity of nigrin b compared with ricin has been at least in part explained by a higher degradation of nigrin b by cells, with a resulting lower concentration remaining inside the cells, and by the different intracellular pathways followed by the two lectins". Thus it is clear that the genus of RIPs is heterogeneous, unpredictable, and complicated in the mechanism of action. Applicant's claimed scope of any heteromeric RIP toxin, such that mutations thereto that result in changed receptor specificity from that of wild type toxin, and such that a population of screening cells would be killed or inhibited to a greater degree, than by the wild type toxin, represent only an invitation to experiment with the genus of RIP (see also above concerning written description and references and cases cited therein). In view of the uncertainty in the art, extrapolation from cytotoxicity data (see Specification at Example 4, pp. 22-23) that a mutated RIP has a different receptor-binding specificity is unpredictable.

(6-7) The level of one or ordinary skill: The level of skill would be high, most likely at the Ph.D. level. However, such persons of ordinary skill in this art, *given its unpredictability*, would have to engage in undue (non-routine) experimentation to carry out the invention as claimed.

(8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure: The claims contain only broad recitations of "heteromeric protein toxin that is a ribosome inactivation protein" and mutant variant protein toxins having "a different receptor-binding specificity". However, the instant

specification does not provide to one skilled in the art a reasonable amount of guidance with respect to the direction in which the experimentation should proceed in carrying out the full scope of the claimed methods. Note that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. *In re Vaeck*, 947 F.2d 488, 496 and n.23, 20 USPQ2d 1438, 1455 and n.23 (Fed. Cir. 1991). Therefore, it is deemed that further research of an unpredictable nature would be necessary to make or use the invention as claimed. Thus, due to the inadequacies of the instant disclosure, undue experimentation would be required of one of ordinary skill in the art to practice the full scope of the claimed invention.

***Claim Rejections - 35 USC § 112, Second Paragraph***

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

16. Claims 1-16, 42 and 43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is maintained for the reasons of record as set forth in the previous Office action. The rejection is copied below for the convenience of the reader.

This rejection over new claim 43 is necessitated by applicant's amendments to the claims. This rejection is maintained for the reasons of record as set forth in the previous Office action. The rejection is copied below for the convenience of the reader.

Claim 1, and its dependent claims, recite the language "different receptor-binding specificity", which renders the claims vague and indefinite because the phrase might mean "specific for a different receptor", or "receptor binding that is different" (but where the receptor remains the same). Because the language is capable of more than one meaning, the claims are rendered indefinite.

Applicant argues that the claim language is intended to encompass both meanings.

#### Response to Arguments

Applicant's arguments entered, 11/21/2005, have been fully considered but they are not persuasive. Whether applicant intends that the claim language is intended to encompass both meanings does not prevent the claims from being vague and indefinite, because it is not clear that both meanings are intended, or if one or the other meaning is meant.

#### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

Art Unit: 1639

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

17. Claims 1-3, 5, 8-13, and 16 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Jackson et al.**, J. of Bacteriology, Feb. 1990, Vol. 172, No. 2, pp. 653-658, (previously cited) and **Kasturi et al.**, J. of Biol. Chem. 15 November 1992, Vol. 267, No. 32, pp. 23427-23433. This rejection is necessitated by applicant's amendments to the claims.

The claims are drawn to a method for making a cytotoxic mutant protein or pool of proteins from a cytotoxic wild type protein said mutant protein or pool of proteins having a different receptor-binding specificity than the wild type protein, comprising: (A) selecting a heteromeric protein toxin having a toxic domain or subunit and a binding domain or subunit, wherein the heteromeric protein toxin is a ribosome inactivating protein; (B) incorporating mutations into DNA encoding the binding domain or subunit of the heteromeric protein toxin to produce a plurality of variant forms of the heteromeric protein toxin; (C) generating a library of microorganism clones producing variant forms of the heteromeric protein toxin; D) screening the variant forms of the heteromeric

protein toxin of said library against a population of screening cells by isolating clones or pools of clones producing said variant forms of the heteromeric protein toxin, treating preparations of said population of screening cells with variant forms of the heteromeric protein toxin produced by the isolated clones or pools of clones, observing the treated preparations of said population of screening cells for toxicity, and selecting, based on the observation of toxicity, a cytotoxic mutant protein or pool of cytotoxic mutant proteins that inhibits or kills said population of screening cells to a greater extent than the wild-type cytotoxic protein, whereby said selected mutant protein or pool of proteins has a different receptor binding specificity than the wild-type binding protein; and (E) making additional copies of the selected cytotoxic mutant protein or pool of proteins, and variations thereof.

Jackson et al., throughout the publication, and especially at the abstract, teach making a cytotoxic mutant protein from a cytotoxic wild type protein that is Shiga toxin and Shiga-like toxin, said mutant protein or pool of proteins, comprising: (A) selecting a Shiga toxin or Shiga-like toxin having an enzymatic subunit A, reading on a toxic domain or subunit and a binding subunit B; (B) incorporating random mutations into DNA encoding the binding subunit B of Shiga toxin and Shiga-like toxin protein toxin to produce a plurality of variant forms of the heteromeric protein toxin, (Specification at p. 654, para 1 and Table 1, p. 655); (C) generating a library of microorganism clones producing variant forms of the heteromeric protein toxin, (Specification at p. 654, para 2 and Table 1, p. 655); D) screening the variant forms of the heteromeric protein toxin of said library against a population of screening cells that are Vero cells or HeLa cells, as

Art Unit: 1639

in Table 2, p.656 (see also p. 654-655, bridging paragraph, "Microcytotoxicity Assay"), by isolating clones or pools of clones producing said variant forms of the heteromeric protein toxin (p. 654-655, bridging paragraph, "Microcytotoxicity Assay"), treating preparations of said population of screening cells with variant forms of the heteromeric protein toxin, (e.g., D16N, D17N, as in Table 2, and compared to wild type protein toxin pEW 3.0); and (E) making additional copies of the selected cytotoxic mutant protein or pool of proteins (Table 4, p. 657, para 1).

Jackson et al. teach mutations to the B subunit of Shiga toxin and Shiga-like toxin. The Office does not have the facilities and resources to provide the factual evidence needed in order to determine whether the mutant protein toxin variant disclosed by Jackson et al. have a different receptor-binding specificity than the wild type protein.

Jackson et al. does not select mutant based upon the observation of toxicity; and wherein the mutations are randomly incorporated (as in new claim 43).

**Kasturi et al.**, J. of Biol. Chem. 15 November 1992, Vol. 267, No. 32, pp. 23427-23433, throughout the publication, and at pp. 23428-23429, Table II and Figure 2, teach selecting mutant *Pseudomonas* exotoxin based upon the observation of cytotoxicity performed on mouse L929 cells and on human A431 and MCF7 cells, including increasing cytotoxicity. Kasturi et al., at p. 23428, para 2, teach the random incorporations of mutations, as evidenced by Kunkel, Proc. Natl. Acad. Sci. U.S.A. 1985, Vol. 82, pp. 488-492.

It would have been *prima facie* obvious, at the time the invention was made, for one of ordinary skill in the art to have used methods for making a cytotoxic mutant ribosome inactivating protein, wherein mutants are selected based upon the observation of toxicity; and wherein the mutations are randomly incorporated (as in new claim 43).

One of ordinary skill in the art would have been motivated to have used methods for making a cytotoxic mutant ribosome inactivating protein or pool of proteins from a cytotoxic wild type protein said mutant protein or pool of proteins having a different receptor-binding specificity than the wild type protein, wherein mutants are selected based upon the observation of toxicity in order to evaluate the functional effect of mutations, as taught by Kasturi et al.; and to use methods of making mutations by random incorporation, in order to generate a variety of mutants for screening, as taught by Kasturi et al., (as in new claim 43).

One of ordinary skill in the art would have had a reasonable expectation of success in selecting mutant proteins, based upon cytotoxicity assay, because such methods were known in the art, as taught by Kasturi et al. One of ordinary skill in the art would have had a reasonable expectation of success in making mutations by random incorporation, because Kasturi et al., teach that such methods were well-known in the art.

18. Claims 1-3, 5, 8-13, and 16 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Tyrrell et al.**, Proc. Natl. Acad. Sci. USA, vol. 89, pp. 524-528, Jan

1992 (IDS filed 11/20/2000), (previously cited) and **Kasturi et al.**, J. of Biol. Chem. 15 November 1992, Vol. 267, No. 32, pp. 23427-23433. This rejection is necessitated by applicant's amendments to the claims.

**Tyrrell et al.**, throughout the publication, and especially at the abstract, p. 524, teach the verotoxin, or Shiga-like toxin, family is a group of subunit toxins, with an A subunit and a B binding subunit and teach the site-directed mutagenesis of the B subunit; teach generating a library of E. coli that produced variant forms of the toxin, wherein the variant toxins include random mutations at position 18, among other targeted amino acids, as shown in fig. 1 and Table 1; wherein microorganisms were expanded and the variant toxins that each clone produces were extracted and screened in cytotoxicity assays using Vero cells, MRC-5 cells and HEp-2 tumor cells; and at p. 528, Fig. 4, teach the mutant toxin GT3 kills more HEp-2 cells than the wild-type toxin. Tyrrell, at, for example, the abstract, teach mutating the B subunit of Shiga-like family toxin that results in a change in the glycosphingolipid receptor specificity.

Tyrrell et al., does not select mutant based upon the observation of toxicity.

**Kasturi et al.**, J. of Biol. Chem. 15 November 1992, Vol. 267, No. 32, pp. 23427-23433, throughout the publication, and at pp. 23428-23429, Table II and Figure 2, teach selecting mutant *Pseudomonas* exotoxin based upon the observation of cytotoxicity performed on mouse L929 cells and on human A431 and MCF7 cells, including increasing cytotoxicity. Kasturi et al., at p. 23428, para 2, teach the random incorporations of mutations, as evidenced by Kunkel, Proc. Natl. Acad. Sci. U.S.A. 1985, Vol. 82, pp. 488-492.

It would have been *prima facie* obvious, at the time the invention was made, for one of ordinary skill in the art to have used methods for making a cytotoxic mutant ribosome inactivating protein, wherein mutants are selected based upon the observation of toxicity; and wherein the mutations are randomly incorporated (as in new claim 43).

One of ordinary skill in the art would have been motivated to have used methods for making a cytotoxic mutant ribosome inactivating protein or pool of proteins from a cytotoxic wild type protein said mutant protein or pool of proteins having a different receptor-binding specificity than the wild type protein, wherein mutants are selected based upon the observation of toxicity in order to evaluate the functional effect of mutations, as taught by Kasturi et al.; and to use methods of making mutations by random incorporation, in order to generate a variety of mutants for screening, as taught by Kasturi et al., (as in new claim 43).

One of ordinary skill in the art would have had a reasonable expectation of success in selecting mutant proteins, based upon cytotoxicity assay, because such methods were known in the art, as taught by Kasturi et al. One of ordinary skill in the art would have had a reasonable expectation of success in making mutations by random incorporation, because Kasturi et al., teach that such methods were well-known in the art.

19. Claims 1-3, 5, 8-13, and 16 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Jackson et al.**, J. of Bacteriology, Feb. 1990, Vol. 172, No. 2, pp.

653-658, (previously cited) and **Van Rie et al.**, US 5,659,123 A. This rejection is necessitated by applicant's amendments to the claims.

**Jackson et al.**, throughout the publication, and especially at the abstract, teach making a cytotoxic mutant protein from a cytotoxic wild type protein that is Shiga toxin and Shiga-like toxin, said mutant protein or pool of proteins, comprising: (A) selecting a Shiga toxin or Shiga-like toxin having an enzymatic subunit A, reading on a toxic domain or subunit and a binding subunit B; (B) incorporating random mutations into DNA encoding the binding subunit B of Shiga toxin and Shiga-like toxin protein toxin to produce a plurality of variant forms of the heteromeric protein toxin, (Specification at p. 654, para 1 and Table 1, p. 655); (C) generating a library of microorganism clones producing variant forms of the heteromeric protein toxin, (Specification at p. 654, para 2 and Table 1, p. 655); D) screening the variant forms of the heteromeric protein toxin of said library against a population of screening cells that are Vero cells or HeLa cells, as in Table 2, p.656 (see also p. 654-655, bridging paragraph, "Microcytotoxicity Assay"), by isolating clones or pools of clones producing said variant forms of the heteromeric protein toxin (p. 654-655, bridging paragraph, "Microcytotoxicity Assay"), treating preparations of said population of screening cells with variant forms of the heteromeric protein toxin, (e.g., D16N, D17N, as in Table 2, and compared to wild type protein toxin pEW 3.0); and (E) making additional copies of the selected cytotoxic mutant protein or pool of proteins (Table 4, p. 657, para 1).

Jackson et al. teach mutations to the B subunit of Shiga toxin and Shiga-like toxin. The Office does not have the facilities and resources to provide the factual

evidence needed in order to determine whether the mutant protein toxin variant disclosed by Jackson et al. have a different receptor-binding specificity than the wild type protein.

Jackson et al. does not select mutant based upon the observation of toxicity.

**Van Rie et al.**, US 5,659,123 A, throughout the patent, and at col. 9, line 9-col. 20, line 16, teach selecting mutant CryIIIA protein toxin based upon the observation of cytotoxicity performed on *Diabrotica virgifera virgifera* larvae mortality, including increasing cytotoxicity. Van Rie et al., at col. 18, line 36-col. 19, line 8, teach the random incorporations of mutations.

It would have been *prima facie* obvious, at the time the invention was made, for one of ordinary skill in the art to have used methods for making a cytotoxic mutant ribosome inactivating protein, wherein mutants are selected based upon the observation of toxicity; and wherein the mutations are randomly incorporated (as in new claim 43).

One of ordinary skill in the art would have been motivated to have used methods for making a cytotoxic mutant ribosome inactivating protein or pool of proteins from a cytotoxic wild type protein said mutant protein or pool of proteins having a different receptor-binding specificity than the wild type protein, wherein mutants are selected based upon the observation of toxicity in order to evaluate the functional effect of mutations, as taught by Van Rie et al.; and to use methods of making mutations by random incorporation, in order to generate a variety of mutants for screening, as taught by Van Rie et al., (as in new claim 43).

One of ordinary skill in the art would have had a reasonable expectation of success in selecting mutant proteins, based upon cytotoxicity assay, because such methods were known in the art, as taught by Van Rie et al. One of ordinary skill in the art would have had a reasonable expectation of success in making mutations by random incorporation, because Van Rie et al., teach that such methods were well-known in the art.

20. Claims 1-3, 5, 8-13, and 16 and 43 are rejected under 35 U.S.C. 102(b) as being anticipated by **Tyrrell et al.**, Proc. Natl. Acad. Sci. USA, vol. 89, pp. 524-528, Jan 1992 (IDS filed 11/20/2000), (previously cited) and **Van Rie et al.**, US 5,659,123 A. This rejection is necessitated by applicant's amendments to the claims.

**Tyrrell et al.**, throughout the publication, and especially at the abstract, p. 524, teach the verotoxin, or Shiga-like toxin, family is a group of subunit toxins, with an A subunit and a B binding subunit and teach the site-directed mutagenesis of the B subunit; teach generating a library of E. coli that produced variant forms of the toxin, wherein the variant toxins include random mutations at position 18, among other targeted amino acids, as shown in fig. 1 and Table 1; wherein microorganisms were expanded and the variant toxins that each clone produces were extracted and screened in cytotoxicity assays using Vero cells, MRC-5 cells and HEp-2 tumor cells; and at p. 528, Fig. 4, teach the mutant toxin GT3 kills more HEp-2 cells than the wild-type toxin.

Tyrrell, at, for example, the abstract, teach mutating the B subunit of Shiga-like family toxin that results in a change in the glycosphingolipid receptor specificity.

Jackson et al. does not select mutant based upon the observation of toxicity.

**Van Rie et al.**, US 5,659,123 A, throughout the patent, and at col. 9, line 9-col. 20, line 16, teach selecting mutant CryIIIA protein toxin based upon the observation of cytotoxicity performed on *Diabrotica virgifera virgifera* larvae mortality, including increasing cytotoxicity. Van Rie et al., at col. 18, line 36-col. 19, line 8, teach the random incorporations of mutations.

It would have been *prima facie* obvious, at the time the invention was made, for one of ordinary skill in the art to have used methods for making a cytotoxic mutant ribosome inactivating protein, wherein mutants are selected based upon the observation of toxicity; and wherein the mutations are randomly incorporated (as in new claim 43).

One of ordinary skill in the art would have been motivated to have used methods for making a cytotoxic mutant ribosome inactivating protein or pool of proteins from a cytotoxic wild type protein said mutant protein or pool of proteins having a different receptor-binding specificity than the wild type protein, wherein mutants are selected based upon the observation of toxicity in order to evaluate the functional effect of mutations, as taught by Van Rie et al.; and to use methods of making mutations by random incorporation, in order to generate a variety of mutants for screening, as taught by Van Rie et al., (as in new claim 43).

One of ordinary skill in the art would have had a reasonable expectation of success in selecting mutant proteins, based upon cytotoxicity assay, because such

Art Unit: 1639

methods were known in the art, as taught by Van Rie et al. One of ordinary skill in the art would have had a reasonable expectation of success in making mutations by random incorporation, because Van Rie et al., teach that such methods were well-known in the art.

21. Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over the pair of **Jackson et al.**, J. of Bacteriology, Feb. 1990, Vol. 172, No. 2, pp. 653-658, (previously cited) and **Kasturi et al.**, J. of Biol. Chem. 15 November 1992, Vol. 267, No. 32, pp. 23427-23433 or the pair of **Tyrrell et al.**, Proc. Natl. Acad. Sci. USA, vol. 89, pp. 524-528, Jan 1992 (IDS filed 11/20/2000), (previously cited) and **Kasturi et al.**, J. of Biol. Chem. 15 November 1992, Vol. 267, No. 32, pp. 23427-23433, each pair taken separately, and as applied to claims 1-3, 5, 8-13, and 16 and 43 above, and further in view of **Cheng et al.**, (US 5,869,250). This rejection is necessitated by applicant's amendments to the claims.

Claims 1 and 4 are drawn to the method of claim 1, wherein the library of microorganism clones producing the variant forms of heteromeric protein toxins comprises yeast or yeast supernatants.

**Jackson et al.**, J. of Bacteriology, Feb. 1990, Vol. 172, No. 2, pp. 653-658, (previously cited) and **Kasturi et al.**, are relied upon, as above. **Tyrrell et al.**, and **Kasturi et al.**, are relied upon, as above.

Jackson and Kasturi et al., or Tyrrell et al. and Kasturi et al., each pair taken separately, do not teach a library of microorganism clones producing the variant forms of heteromeric protein toxins that comprises yeast or yeast supernatants.

**Cheng et al.**, (US 5,869,250), throughout the patent and especially at col. 4, lines 31-44, teach construction of a combinatorial library for expression in yeast.

It would have been *prima facie* obvious at the time the invention was made for one of ordinary skill in the art to have used a library of microorganism clones producing variant forms of heteromeric protein toxins that comprises yeast or yeast supernatants in methods for making cytotoxic mutant proteins having different receptor-binding specificity than the wild type protein.

One of ordinary skill in the art would have been motivated to use a library of microorganism clones that comprises yeast or yeast supernatants because Cheng et al. teach that yeast can express a large number of peptides from combinatorial libraries.

22. Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over the pair of **Jackson et al.**, J. of Bacteriology, Feb. 1990, Vol. 172, No. 2, pp. 653-658, (previously cited) and **Van Rie et al.**, US 5,659,123 A or the pair of **Tyrrell et al.**, Proc. Natl. Acad. Sci. USA, vol. 89, pp. 524-528, Jan 1992 (IDS filed 11/20/2000), (previously cited) and **Van Rie et al.**, US 5,659,123 A, each pair taken separately, and as applied to claims 1-3, 5, 8-13, and 16 and 43 above, and further in view of **Cheng et al.**, (US 5,869,250). This rejection is necessitated by applicant's amendments to the claims.

**Jackson et al.**, J. of Bacteriology, Feb. 1990, Vol. 172, No. 2, pp. 653-658, (previously cited) and **Van Rie et al.**, are relied upon, as above. **Tyrrell et al.**, and **Van Rie et al.**, are relied upon, as above.

Jackson and Van Rie et al., or Tyrrell et al. and Van Rie et al., each pair taken separately, do not teach a library of microorganism clones producing the variant forms of heteromeric protein toxins that comprises yeast or yeast supernatants.

**Cheng et al.**, (US 5,869,250), throughout the patent and especially at col. 4, lines 31-44, teach construction of a combinatorial library for expression in yeast.

It would have been *prima facie* obvious at the time the invention was made for one of ordinary skill in the art to have used a library of microorganism clones producing variant forms of heteromeric protein toxins that comprises yeast or yeast supernatants in methods for making cytotoxic mutant proteins having different receptor-binding specificity than the wild type protein.

One of ordinary skill in the art would have been motivated to use a library of microorganism clones that comprises yeast or yeast supernatants because Cheng et al. teach that yeast can express a large number of peptides from combinatorial libraries.

23. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over the pair of **Jackson et al.**, J. of Bacteriology, Feb. 1990, Vol. 172, No. 2, pp. 653-658, (previously cited) and **Kasturi et al.**, J. of Biol. Chem. 15 November 1992, Vol. 267, No. 32, pp. 23427-23433 or the pair of **Tyrrell et al.**, Proc. Natl. Acad. Sci. USA, vol. 89, pp. 524-

528, Jan 1992 (IDS filed 11/20/2000), (previously cited) and **Kasturi et al.**, J. of Biol. Chem. 15 November 1992, Vol. 267, No. 32, pp. 23427-23433, each pair taken separately, and as applied to claims 1-3, 5, 8-13, and 16 and 43 above, and further in view of **Reidhaar-Olson et al.**, Meth Enzymol (1991), vol. 208: 564-586. This rejection is necessitated by applicant's amendments to the claims.

Claims 1 and 6 are drawn to the method of claim 1, wherein said mutation is incorporated into said binding domain or subunit by use of a combinatorial cassette method comprising: (A) preparing synthetic mutant oligonucleotides capable of annealing with a corresponding wild type oligonucleotide from said binding domain or subunit; (B) annealing said synthetic oligonucleotide from said binding domain or subunit to an overlapping wild type oligonucleotide to form a double stranded sequence; (C) creating a combinatorial cassette by mutually primed synthesis of said double stranded sequence; and (D) incorporating said cassette into a vector containing a gene for said toxin.

**Jackson et al.**, J. of Bacteriology, Feb. 1990, Vol. 172, No. 2, pp. 653-658, (previously cited) and **Kasturi et al.**, are relied upon, as above. **Tyrrell et al.**, and **Kasturi et al.**, are relied upon, as above.

Jackson and Kasturi et al., or Tyrrell et al. and Kasturi et al., each pair taken separately, do not teach a combinatorial cassette method.

**Reidhaar-Olson et al.**, throughout the reference, and at pp. 564-571 and 575-577, teach random mutagenesis of protein sequences using cassette mutagenesis,

including mutating a single codon to encode all naturally occurring amino acids, which reads on a combinatorial cassette method.

It would have been *prima facie* obvious at the time the invention was made for one of ordinary skill in the art to have used a combinatorial cassette in methods for making cytotoxic mutant proteins having different receptor-binding specificity than the wild type protein.

One of ordinary skill in the art would have been motivated to use a combinatorial cassette method in making cytotoxic mutant proteins because Reidhaar-Olson et al. teach the use of oligonucleotide cassettes to generate protein variants having random mutations.

24. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over the pair of **Jackson et al.**, J. of Bacteriology, Feb. 1990, Vol. 172, No. 2, pp. 653-658, (previously cited) and **Van Rie et al.**, US 5,659,123 A or the pair of **Tyrrell et al.**, Proc. Natl. Acad. Sci. USA, vol. 89, pp. 524-528, Jan 1992 (IDS filed 11/20/2000), (previously cited) and **Van Rie et al.**, US 5,659,123 A, each pair taken separately, and as applied to claims 1-3, 5, 8-13, and 16 and 43 above, and further in view of **Reidhaar-Olson et al.**, Meth Enzymol (1991), vol. 208: 564-586. This rejection is necessitated by applicant's amendments to the claims.

**Jackson et al.**, J. of Bacteriology, Feb. 1990, Vol. 172, No. 2, pp. 653-658, (previously cited) and **Kasturi et al.**, are relied upon, as above. **Tyrrell et al.**, and **Kasturi et al.**, are relied upon, as above.

Jackson and Van Rie et al., or Tyrrell et al. and Van Rie et al., each pair taken separately, do not teach a combinatorial cassette method.

**Reidhaar-Olson et al.**, throughout the reference, and at pp. 564-571 and 575-577, teach random mutagenesis of protein sequences using cassette mutagenesis, including mutating a single codon to encode all naturally occurring amino acids, which reads on a combinatorial cassette method.

It would have been *prima facie* obvious at the time the invention was made for one of ordinary skill in the art to have used a combinatorial cassette in methods for making cytotoxic mutant proteins having different receptor-binding specificity than the wild type protein.

One of ordinary skill in the art would have been motivated to use a combinatorial cassette method in making cytotoxic mutant proteins because Reidhaar-Olson et al. teach the use of oligonucleotide cassettes to generate protein variants having random mutations.

25. Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over the pair of **Jackson et al.**, J. of Bacteriology, Feb. 1990, Vol. 172, No. 2, pp. 653-658, (previously cited) and **Kasturi et al.**, J. of Biol. Chem. 15 November 1992, Vol. 267, No. 32, pp.

23427-23433 or the pair of **Tyrrell et al.**, Proc. Natl. Acad. Sci. USA, vol. 89, pp. 524-528, Jan 1992 (IDS filed 11/20/2000), (previously cited) and **Kasturi et al.**, J. of Biol. Chem. 15 November 1992, Vol. 267, No. 32, pp. 23427-23433, each pair taken separately, and as applied to claims 1-3, 5, 8-13, and 16 and 43 above, and further in view of **Nickoloff et al.**, (US 5,354,670). This rejection is necessitated by applicant's amendments to the claims.

Claims 1 and 7 are drawn to the method of claim 1 wherein said mutation is incorporated into said binding domain subunit by means of a unique site elimination method of mutagenesis.

**Jackson et al.**, J. of Bacteriology, Feb. 1990, Vol. 172, No. 2, pp. 653-658, (previously cited) and **Kasturi et al.**, are relied upon, as above. **Tyrrell et al.**, and **Kasturi et al.**, are relied upon, as above.

Jackson and Kasturi et al., or Tyrrell et al. and Kasturi et al., each pair taken separately, do not teach incorporation of mutations into the binding domain subunit by a unique site elimination method.

**Nickoloff et al.**, (US 5,354,670), et al., throughout the patent, and especially at col. 2, line 2-col. 8, line 10, teach a method of site-specific mutagenesis of DNA that can be used to mutagenize DNA, especially circular DNA, so that parental DNA, containing nonessential, unique restriction site, is used to generate progeny DNA containing the desired mutation but lacking the restriction site.

It would have been *prima facie* obvious at the time the invention was made for one of ordinary skill in the art to have used unique site elimination (USE) methods for

Art Unit: 1639

making cytotoxic mutant proteins having different receptor-binding specificity than the wild type protein.

One of ordinary skill in the art would have been motivated to use unique site elimination (USE) methods in making cytotoxic mutant proteins because Nickoloff et al. teach the use of USE methods to mutagenize DNA at particular sites.

26. Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over the pair of **Jackson et al.**, J. of Bacteriology, Feb. 1990, Vol. 172, No. 2, pp. 653-658, (previously cited) and **Van Rie et al.**, US 5,659,123 A or the pair of **Tyrrell et al.**, Proc. Natl. Acad. Sci. USA, vol. 89, pp. 524-528, Jan 1992 (IDS filed 11/20/2000), (previously cited) and **Van Rie et al.**, US 5,659,123 A, each pair taken separately, and as applied to claims 1-3, 5, 8-13, and 16 and 43 above, and further in view of **Nickoloff et al.**, (US 5,354,670). This rejection is necessitated by applicant's amendments to the claims.

**Jackson et al.**, J. of Bacteriology, Feb. 1990, Vol. 172, No. 2, pp. 653-658, (previously cited) and **Van Rie et al.**, are relied upon, as above. **Tyrrell et al.**, and **Van Rie et al.**, are relied upon, as above.

Jackson and Van Rie et al., or Tyrrell et al. and Van Rie et al., each pair taken separately, do not teach incorporation of mutations into the binding domain subunit by a unique site elimination method.

**Nickoloff et al.**, (US 5,354,670), et al., throughout the patent, and especially at col. 2, line 2-col. 8, line 10, teach a method of site-specific mutagenesis of DNA that can

be used to mutagenize DNA, especially circular DNA, so that parental DNA, containing nonessential, unique restriction site, is used to generate progeny DNA containing the desired mutation but lacking the restriction site.

It would have been *prima facie* obvious at the time the invention was made for one of ordinary skill in the art to have used unique site elimination (USE) methods for making cytotoxic mutant proteins having different receptor-binding specificity than the wild type protein.

One of ordinary skill in the art would have been motivated to use unique site elimination (USE) methods in making cytotoxic mutant proteins because Nickoloff et al. teach the use of USE methods to mutagenize DNA at particular sites.

27. Claims 2, and 13-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over the pair of **Jackson et al.**, J. of Bacteriology, Feb. 1990, Vol. 172, No. 2, pp. 653-658, (previously cited) and **Kasturi et al.**, J. of Biol. Chem. 15 November 1992, Vol. 267, No. 32, pp. 23427-23433 or the pair of **Tyrrell et al.**, Proc. Natl. Acad. Sci. USA, vol. 89, pp. 524-528, Jan 1992 (IDS filed 11/20/2000), (previously cited) and **Kasturi et al.**, J. of Biol. Chem. 15 November 1992, Vol. 267, No. 32, pp. 23427-23433, each pair taken separately, and as applied to claims 1-3, 5, 8-13, and 16 and 43 above, and further in view of **Frankel et al.**, (US 4,753,894). This rejection is necessitated by applicant's amendments to the claims.

Claims 1, 2, and 13-15 are drawn to the method of claim 1 wherein the screening cells are breast cancer cells and that are SK BR-3 or CAMA-I. Claim 42 is drawn to the method of claim 1, wherein the screening cells are insensitive to the wild-type cytotoxic protein.

**Jackson et al.**, J. of Bacteriology, Feb. 1990, Vol. 172, No. 2, pp. 653-658, (previously cited) and **Kasturi et al.**, are relied upon, as above. **Tyrrell et al.**, and **Kasturi et al.**, are relied upon, as above.

Jackson and Kasturi et al., or Tyrrell et al. and Kasturi et al., each pair taken separately, do not teach screening cells that are breast cancer cells and are SK BR-3 or CAMA-I.

**Frankel et al.**, (US 4,753,894) et al., throughout the patent, and especially at col. 3, lines 46-57, teach testing antibodies (where different antibodies have different antigen specificities) conjugated to ricin toxin in cytotoxicity assays using CAMA-1 and SKBR-3 breast tumor cells.

It would have been *prima facie* obvious at the time the invention was made for one of ordinary skill in the art to have tested cytotoxic mutant proteins in cytotoxicity assays comprising CAMA-1 and SKBR-3 breast tumor cells, and wherein the screening cells are insensitive to the wild-type cytotoxic protein, (as in claim 42), because CAMA-1 inherently lacks the CD77 marker, as evidenced by the Specification at p. 12, lines 16-19.

One of ordinary skill in the art would have been motivated to screen cytotoxic mutant proteins having different receptor-binding specificity than the wild type protein

because CAMA-1 and SKBR-3 breast tumor cells are an art-recognized *in vitro* model system for selecting anti-cancer agents, including those comprising a ricin protein toxin, as taught by Frankel et al.

28. Claims 2 and 13-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over the pair of **Jackson et al.**, J. of Bacteriology, Feb. 1990, Vol. 172, No. 2, pp. 653-658, (previously cited) and **Van Rie et al.**, US 5,659,123 A or the pair of **Tyrrell et al.**, Proc. Natl. Acad. Sci. USA, vol. 89, pp. 524-528, Jan 1992 (IDS filed 11/20/2000), (previously cited) and **Van Rie et al.**, US 5,659,123 A, each pair taken separately, and as applied to claims 1-3, 5, 8-13, and 16 and 43 above, and further in view of **Frankel et al.**, (US 4,753,894). This rejection is necessitated by applicant's amendments to the claims.

Claims 1, 2, and 13-15 are drawn to the method of claim 1 wherein the screening cells are breast cancer cells and that are SK BR-3 or CAMA-I. Claim 42 is drawn to the method of claim 1, wherein the screening cells are insensitive to the wild-type cytotoxic protein.

**Jackson et al.**, J. of Bacteriology, Feb. 1990, Vol. 172, No. 2, pp. 653-658, (previously cited) and **Van Rie et al.**, are relied upon, as above. **Tyrrell et al.**, and **Van Rie et al.**, are relied upon, as above.

Jackson and Van Rie et al., or Tyrrell et al. and Van Rie et al., each pair taken separately, do not teach screening cells that are breast cancer cells and are SK BR-3 or CAMA-I.

**Frankel et al.**, (US 4,753,894) et al., throughout the patent, and especially at col. 3, lines 46-57, teach testing antibodies (where different antibodies have different antigen specificities) conjugated to ricin toxin in cytotoxicity assays using CAMA-1 and SKBR-3 breast tumor cells.

It would have been *prima facie* obvious at the time the invention was made for one of ordinary skill in the art to have tested cytotoxic mutant proteins in cytotoxicity assays comprising CAMA-1 and SKBR-3 breast tumor cells, and wherein the screening cells are insensitive to the wild-type cytotoxic protein, (as in claim 42), because CAMA-1 inherently lacks the CD77 marker, as evidenced by the Specification at p. 12, lines 16-19.

One of ordinary skill in the art would have been motivated to screen cytotoxic mutant proteins having different receptor-binding specificity than the wild type protein because CAMA-1 and SKBR-3 breast tumor cells are an art-recognized *in vitro* model system for selecting anti-cancer agents, including those comprising a ricin protein toxin, as taught by Frankel et al.

### **Conclusion**

29. Claims 1-7, 9-16, 42 and 43 stand finally rejected.

30. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

31. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Shibuya whose telephone number is (571) 272-0806. The examiner can normally be reached on M-F, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.


Art Unit: 1639

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Mark L. Shibuya  
Examiner  
Art Unit 1639

ms



RAJESH KUMAR  
PATENT EXAMINER